MEDICAL PROGRESS:

Progress in the Management of Syphilis

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SINCE the discovery in 1943 that penicillin was an effective therapeutic agent in syphilis, treatment methods of the disease have been completely revolutionized. Syphilotherapy is in a state of great influx. It will take several years and much cooperative experience and study to learn how best to utilize penicillin in treating syphilis. This discussion is an attempt to present some of the fundamentals related to the use of penicillin in the successful management of the syphilis patient.

DIAGNOSIS

The accurate diagnosis of syphilis is not always easy. Preferably it should not be based solely upon one or two serologic tests for syphilis. Many mistakes in diagnosis have been made because of the occurrence of non-specific positive serologic tests. A diagnosis of latent syphilis needs not be made in haste. The condition is not a medical emergency although many physicians are inclined to look upon the positive blood test as a signal for the immediate institution of treatment.

Shaffer[11] states that non-specific positive serologic tests for syphilis were considered rare in the past except in a few diseases such as yaws, leprosy, and malaria. Recent experience is emphasizing the fact that such non-specific reactions are numerous, particularly with precipitation or flocculation tests (Kahn, Kline, Eagle, Mazzini). Some of the more recent additions to the list of conditions which may cause false positive tests are many febrile and toxic states, vaccinations, serums, virus pharyngitis and bronchitis, atypical pneumonia, infectious mononucleosis, undulant fever, chancroid and lymphogranuloma venereum. Certain individuals are carriers of non-specific reactions, usually of low or fluctuating titer, which may persist seemingly throughout life. A generally accepted method of differentiation between non-specific and specific reactions by any one serologic procedure is not available at present. Verification tests are inconclusive. Davis[4] states that any febrile disease occurring within three months preceding the test may be suspected as the cause of a false positive reaction. Transient false positive tests may appear in the absence of demonstrable disease of any kind and in some cases may persist for a long time. The quantitative S.T.S.* is an aid in differentiating non-specific tests. Most false positive blood tests are either of short duration (days to several weeks) or of low titer when quantitative serologic tests are performed. False positive tests of high titer will usually decrease materially over a period of several days. Most false positive tests can be revealed by serial quantitative serologic examination carried out over a period of several days to a few weeks.

Just as a positive serologic test without the presence of other clinical manifestations of the disease is a challenge to rule out syphilis, the opposite is true when lesions are present. Genital lesions which offer the faintest possibility of being syphilitic should be considered so until proven otherwise. In lesions which are negative to darkfield examination, the patient may have seronegative primary syphilis even though repeated darkfield tests are negative. In most cases good technique and persistence in repeating darkfield studies will result in the discovery of the spirochete. Obtaining material for darkfield study from regional lymph nodes (the satellite bubo) will frequently result in success where it is impossible to obtain organisms from the primary lesion.

At times one may be confronted with a persistently darkfield negative primary lesion in the presence of a positive blood test. The question arises as to whether this is a case of primary seropositive syphilis or one of latent syphilis complicated by a genital lesion of different etiology such as chancroid or lymphogranuloma venereum. Quantitative serologic tests for syphilis are often a great aid in solving such a problem. According to Heyman,[5] if it is a case of primary syphilis the quantitative titer will rise in a few days, whereas the titer will remain stationary if it is a case of latent syphilis with a genital lesion due to another disease. If the titer falls, the lesion may be due to chancroid or lymphogranuloma venereum which has caused a false positive serologic test. Other conditions in which the quantitative S.T.S. frequently leads to the correct conclusion are as follows:

1. Relapsing syphilis: A progressive rise in titer indicates a relapse. Serologic relapse usually precedes mucocutaneous relapse by approximately one month and often these lesions are so minimal as to go unnoticed. The diagnosis of serologic relapse should not be made unless there is a significant rise in titer which persists upon recheck one to two weeks later.

2. Congenital syphilis of the newborn: In weekly quantitative studies on the infant the titer will rise progressively or remain high if the child is infected. A child may be born with a positive blood test and not be actually infected. This is merely a reflection of the mother's serologic reaction and the titer falls rapidly.

3. Prozone phenomenon: In a few very strongly positive serums, negative reactions will occur in whole serum; however, a positive serologic test will result when the serum is diluted for quantitative study.

Quantitative serologic tests are obtained by per-

* Abbreviation for Serologic Test for Syphilis.

forming tests on serial dilutions of the whole serum, preferably diluting the serum to the point where a positive reaction is no longer obtained. If, for example, a given serum is positive down to a dilution of 1:50 the serologic titer is 50. In the Kahn test this figure may be multiplied by four to obtain the Kahn units (a Kahn titer of 50 indicates 200 Kahn units).

Congenital Syphilis:

In making a diagnosis of congenital syphilis in the newborn without physical evidence of infection, a quantitative blood test should be obtained at birth and every week or two weeks until a positive diagnosis is made or the disease ruled out. In the non-syphilitic infant born with a positive S.T.S. the titer will usually fall to less than 10 Kahn units in two to three weeks and to negativity by eight weeks. In an occasional case a low titer may be maintained for as long as twelve to fourteen weeks. A final serologic test to completely rule out syphilis is indicated at the age of six months. In a child infected with syphilis, an initial high titer will be maintained and at the end of four weeks treatment should be instituted even though there are no other clinical signs of syphilis. Therapy is also indicated in a case of low titer at birth which progressively rises in weekly tests up to the age of one month. Where quantitative serologic tests are not available it is best to treat the child if strongly positive tests are obtained beyond the sixth or eighth week of life. Roentgenograms of the long bones are often helpful. Approximately 90 per cent of untreated syphilitic infants will show evidence of osteochondritis or periostitis in roentgenograms at the age of six to eight weeks.

Asymptomatic Neurosyphilis:

The diagnosis of asymptomatic neurosyphilis is based solely upon examination of the cerebrospinal fluid. All patients upon whom a diagnosis of latent syphilis is made should have a spinal fluid examination at once, as one may not be actually dealing with latent syphilis but with asymptomatic neurosyphilis. It is also advisable to obtain spinal fluid studies early in cases of primary or secondary syphilis, in order to know whether or not the neuraxis has been invaded. Moore and Mohr[7] studied 48 patients with early asymptomatic neurosyphilis and 36 of these cases were still in the primary or secondary stage of syphilis. The cerebrospinal fluid findings in neurosyphilis are classified as follows:

Group I (Minimal changes). The cell count is elevated to 7 or more and/or the protein to 37 mgm. per cent or more. The complement fixation and collodial tests are negative.

Group II (Moderate changes). Cell count and protein are normal or abnormal to any degree. Complement fixation test is positive with relative large amounts of fluid (0.2 cc. to 1.0 cc.). Colloidal curves of any type.

Group III (Maximal changes). Cell count and protein usually elevated. Complement fixation test positive with small amounts of fluid (0.1 cc. or less). Collodial curves usually first zone (paretic) type.

TREATMENT

Penicillin is the most important therapeutic agent in the treatment of syphilis today. As commercially distributed, it is not a single substance but a mixture of several. At least four different penicillin species, which differ chemically in the side chains attached to the basic nuclear structure, have been identified. These are known as penicillins G, X, F and K.[14]

Studies to determine the Treponemicidal effect of these four penicillin fractions indicate that G is the most effective of the fractions so far studied and available. On the basis of present information, it is of utmost importance that a commercial penicillin of high G content, or the crystalline penicillin G itself, be employed in the treatment of syphilis.

Early Syphilis:

Cooperative studies indicate that the minimum dose of penicillin for seronegative primary syphilis be not less than 3.6 million units (60 injections of 60,000 units each given every 3 hours). The recommended minimum dose for seropositive primary syphilis, secondary syphilis, and early latent syphilis of less than two years' duration is not less than 5.4 million units (90 injections of 60,000 units or 60 injections of 90,000 units each.)

If reinfection, infectious or serologic relapse of previously treated early syphilis occurs, the above course should be repeated plus the addition of 360 mg. of oxophenarsine hydrochloride (mapharsen) or an analogue given two to three times weekly in six individual injections of 60 mg. each, plus bismuth subsalicylate given twice weekly in six individual intramuscular injections of 0.2 gm. each.

For a second relapse of early syphilis after previous penicillin treatment, the patient should be placed on metal chemotherapy with arsenic and bismuth, preferably by the 26-week schedule employed by the Army and Navy. (Forty intravenous injections of mapharsen and 16 injections of bismuth subsalicylate.)

The ambulatory treatment of early syphilis utilizing a single daily intramuscular injection of the absorption-delaying calcium penicillin in peanut oil-beeswax is of great economic advantage in that hospitalization of the patient is not required. If calcium penicillin in peanut oil-beeswax is used the recommended average daily dose for an adult is 600,000 units. For early syphilis, a minimum total dose of 4.8 to 6 million units of this preparation is advised.

Latent Syphilis:

Latent syphilis is that stage of syphilitic infection in which the patient presents no physical signs or symptoms of the disease, the spinal fluid has been demonstrated to be normal and a positive serologic test for syphilis is the only indication of infection. Syphilis may be considered late latent when it is of more than two years' duration.

Moore[9] states that the only present rationale for the use of penicillin in previously untreated latent

syphilis is its known effect in patients with early or late active syphilitic disease. Presumably if penicillin will actually "cure" early syphilis, it should be of preventive value in latent syphilis.

The treatment may be given with a minimum of 4 million units of penicillin in aqueous solution (80 injections of 50,000 units every three hours for ten days) or 6 million units of sodium penicillin in peanut oil-beeswax (10 daily injections of 600,000 units each).

It is to be realized that seroresistance is the rule, not the exception, in latent syphilis and that there is no evidence as yet that penicillin is more effective than any other form of treatment in reducing the serologic test for syphilis to negative in these cases.

Syphilis in Pregnancy:

The use of penicillin for the treatment of syphilis in pregnancy has proven to be incomparably superior to metal chemotherapy. The reported treatment results are most favorable no matter what the duration of pregnancy at the time of treatment. Cole et al.[2] report successful results in mother and infant although treatment was not instituted until the last month of pregnancy. The dosage schedules of penicillin are still in the formative stage and require further study, but it is generally agreed that the total dose of commercial penicillin should not be less than 3.6 to 5.4 million units administered over a period of not less than seven and one-half days. Following completion of treatment, monthly clinical examinations and titered serologic tests until delivery are essential. The quantitatively titered serologic test for syphilis is particularly necessary in the proper management of the syphilitic prospective mother and her child.

Re-treatment during pregnancy with penicillin is indicated if there is any evidence of a clinical or serologic relapse or if there is no significant decline in the serologic titer within three months after treatment.

Early Congenital Syphilis:

When the diagnosis of syphilis in the new-born is concluded, immediate treatment is indicated. At present, a total dosage of at least 100,000 to 125,000 units of penicillin per kilogram of body weight, administered every three hours over a period of not less than 12 to 15 days, is considered a satisfactory regime of treatment.

Neurosyphilis:

At present it appears quite certain that, in all types of neurosyphilis, penicillin is superior to any form of metal chemotherapy. The improvement in the serologic reactions of the spinal fluid in neurosyphilis is the outstanding benefit that follows penicillin therapy.

Evidence to date indicates that penicillin alone in a total dosage of 8 to 10 million units administered every three hours over a period of 15 to 21 days may be given in early or late asymptomatic neurosyphilis, acute syphilitic meningitis, vascular and meningovascular neurosyphilis and gumma of the brain or spinal cord. Brunsting[1] states that a small group of patients with neurosyphilis have been given penicillin in peanut oil-beeswax and that the results have been equal to those obtained when patients were given penicillin every three hours around the clock.

If improvement is unsatisfactory or there is evidence of a relapse, either clinical or in the spinal fluid, re-treatment with a combination of fever therapy and penicillin must be given.

The utilization of combined penicillin and fever therapy is advised as the initial treatment of primary optic atrophy, paresis and taboparesis.

Cardiovascular Syphilis:

It is impossible to state at present whether penicillin should or should not be used in the treatment of cardiovascular syphilis. If penicillin is employed, extreme caution must be exercised to avoid therapeutic shock during the first five to seven days of treatment. Information to date provides no evidence as to therapeutic efficacy but serves as a warning that penicillin may do actual harm through therapeutic shock.

POST-TREATMENT OBSERVATION

Serologic tests for syphilis do not become negative immediately following rapid treatment. The progress to negativity takes place over a period of weeks to months and is characterized by a gradual decrease in quantitative serologic titer. It is important and necessary to follow a routine of post-treatment observation to determine the results of treatment. Each patient should be examined every month during the first post-treatment year, every three months during the second year, each six months in the third year, and yearly thereafter. At each visit a thorough search for relapsing mucocutaneous lesions should be made and a blood specimen obtained for a quantitative S.T.S. Cerebrospinal fluid examinations are indicated at either six or twelve months after treatment and another check-up is advisable at the end of two years. Such a routine will determine treatment failures, serologic or infectious relapse, and seroresistance. This assures the patient the greatest possible chance of cure by affording re-treatment at the earliest necessity.

Reduction in blood reagin titer of treated patients is usually greatest by the end of the first or second month.[6] In general, primary cases reach negativity in two to three months; secondary cases in three to six months. In most instances the longer a patient has had syphilis the longer it takes for the serologic test to become negative after treatment.[13] Occasionally complement fixation titers of less than 10 persist for many months after treatment. Such cases should not be considered therapeutic failures. In some cases followed by Thomas, complement fixation tests with titers below 10 persisted for more than three years before becoming entirely negative. However, in most of these patients the titer had fallen below 10 within nine months. In early latent syphilis it will commonly take three or four years to reach seronegativity

after rapid treatment. Many latent cases will be seroresistant and a completely negative blood test will never be attained even though additional treatment is given. The management of seroresistance has been well discussed by Moore.[8] Every physician who sees patients with syphilis should read Moore's excellent presentation. One of the greatest errors in the management of syphilis has been the tendency of many physicians to treat a positive blood test without taking into account the degree of activity of the syphilitic process. There is a point of adequate treatment beyond which no further therapeutic success can be attained. Overtreatment accomplishes nothing and is dangerous to the patient when arsenicals and bismuth are used. Seroresistance in treated latent syphilis is common. A persistently positive blood test in a well treated case of syphilis may represent only the scar which remains of a disease well healed. As Thomas states,[13] the aim of therapy in early syphilis is to attain a negative serologic test, but in late syphilis the purpose of treatment is to prevent the progress of the disease and the development of late symptoms. At present the proper management of most cases of syphilis will consist of a rapid form of treatment utilizing penicillin, followed by post-treatment observation and re-treatment in instances of therapeutic failure, relapse or reinfection.

After rapid treatment of syphilis, any one of the following situations may result:

1. Cure. The S.T.S. gradually becomes negative over a varying period of time and remains permanently negative. All clinical signs of active syphilitic infection disappear. The cerebrospinal fluid is normal one year following treatment.

2. Relapse. The S.T.S. reverts to negative or the complement fixation titer diminishes to low values, usually less than 10. Subsequently, there is a sharp rise in titer which is confirmed by repeated tests indicating serologic relapse, which usually precedes mucocutaneous relapse by about one month.

3. Neuro-relapse. The spinal fluid cells and protein are reduced to normal and the complement fixation titer falls; subsequently, the cells and/or protein increase to abnormal values and there is a rise in complement fixation titer. The blood may be either negative or positive as there is no correlation between the blood reagin titer and central nervous system involvement.

4. Treatment failure. The blood reagin titer remains high or has not decreased significantly by six to twelve months after treatment. In central nervous system involvement the cells and/or protein do not return to normal and/or the complement fixation test remains of high titer.

5. Seroresistance. The blood complement fixation titer falls to low values, usually less than 10, but never becomes completely negative or to rise sharply as in relapse.

6. Reinfection. Definite evidence of cure has been attained followed by the appearance of new darkfield positive lesions of primary syphilis while the blood test is still negative.

Re-treatment:

In a certain percentage of patients who receive rapid treatment, subsequent additional therapy will be required in order to obtain a satisfactory therapeutic response. The type of therapy to be used in these re-treatment cases has been discussed in the foregoing section on treatment. Re-treatment is indicated in relapse, reinfection, and treatment failure.

All patients who relapse either serologically or clinically (recurrence of lesions) should be re-treated immediately. Most instances of relapse in early syphilis occur between the third and ninth post-treatment month. The occurrence of a definite rise in serologic titer over the immediately preceding report at a routine post-treatment examination indicates possible relapse. This titer rise should be maintained or increased in at least two or three repeated blood tests over a two to three weeks period before a diagnosis of relapse is finally concluded. The discovery of recurring lesions, especially when they are darkfield positive, definitely establishes relapse. Usually infectious relapse and reinfection can be distinguished by carefully conducted serologic studies. Rein[10] states that, following penicillin therapy in patients with early syphilis, there is usually a progressive reduction in serologic titer. In reinfection, patients attain and maintain complete seronegativity followed by the development of darkfield positive seronegative lesions at a new site. Shortly afterward there develop seropositive reactions with rapidly increasing titers. In relapse there is noted a sudden increase in serologic titer followed in about one month by clinical evidence of mucocutaneous relapse. By carefully following the patient's serologic titer it is often possible to avoid the development of infectious relapsing lesions.

In some patients there is a lack of the desired serologic response and titers remain high, denoting treatment failure. Thomas[13] states that patients with primary or secondary syphilis who possess complement fixation titers greater than 20, or flocculation titers greater than 32, nine months after rapid treatment should be re-treated. Those with complement fixation titers between 10 and 20 may be observed for further drop in titer or re-treated as a precautionary measure. One should not expect a rapid drop in titer after re-treatment. Patients with normal spinal fluids but persistently low complement fixation titers of less than 10 for more than one year after treatment require no further therapy unless marked and sustained rise in titer (relapse) ensues.

In central nervous system syphilis, according to Thomas,[13] the spinal fluid findings are the fundamental guides to treatment. Indications for re-treatment are: (1) Failure of the cells and protein to become normal within six months; (2) A rise in cells or protein to abnormal values after they have been reduced to normal; or (3) A sustained rise in complement fixation titer after initial reduction. Dattner, Thomas and Wexler[3] state that, if the cell count and protein content of the spinal fluid are reduced to normal by treatment and re-

main so, clinical progression or relapse in asymptomatic neurosyphilis rarely occurs, even though the Wassermann reaction persists unchanged or is only slightly to moderately improved. In most cases the complement fixation titer will be significantly reduced or drop to negative within one to six years without further treatment. Thomas[13] feels that it is a mistake to treat patients for neurosyphilis until the spinal fluid Wassermann test becomes negative.

In discussing relapse in treated neurosyphilis, Stokes and Steiger[12] feel that observations should be carried out for at least one year in the absence of convincing evidence of progression before further treatment measures are adopted.

Moore and Mohr[7] state that penicillin exerts a prompt and dramatic effect on abnormalities of the spinal fluid. Affected in order of promptitude of action are the cell count, protein, colloidal curve and Wassermann reaction. The cell count in both early and late neurosyphilis is usually normal in ten to twenty-four weeks after treatment. The protein usually reaches normal by the sixth month. They feel that the results of penicillin therapy in asymptomatic central nervous system syphilis are exceedingly satisfactory since "activity" as signified by increased cells and protein disappears promptly in practically all cases.

SUMMARY

Syphilotherapy is at present in a state of great flux due primarily to the discovery of penicillin in 1943.

2. Accurate diagnosis is not always easy as recent experience has revealed that non-specific positive serologic reactions are numerous.

3. Quantitative serologic tests for syphilis are valuable in diagnosis and post-treatment observation of syphilis.

4. When penicillin alone is used in the treatment of syphilis large doses should be used.

5. In cases requiring re-treatment the addition of arsenicals and bismuth to the penicillin schedule is advised.

6. Penicillin therapy of syphilis in pregnancy is greatly superior to metal chemotherapy.

7. The serologic test for syphilis does not become negative immediately after treatment. All patients must follow a routine of post-treatment observation.

8. Results of treatment of neurosyphilis with penicillin have been very gratifying.

9. The spinal fluid findings are the fundamental guides to treatment in central nervous system syphilis.

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